

Claims:

1. A spermicidal composition comprising a gel-microemulsion comprising an oil-in-water microemulsion and a polymeric hydrogel, wherein  
the oil-in-water microemulsion comprises a lipid, one or more pharmaceutically acceptable surfactants, one or more pharmaceutically acceptable humectants, and water.
2. The composition of claim 1, wherein one or more of the surfactants are selected from the group consisting of ethoxylated castor oil, block copolymer of ethylene oxide and propylene oxide, and phospholipid.
3. The compound of claim 2, wherein the phospholipid is a purified soybean phospholipid.
4. The compound of claim 2, wherein the phospholipid is a phosphatidylcholine.
5. The composition of claim 1, wherein the surfactant comprises one or more phospholipids and one or more ~~non~~-ionic surfactants.
6. The composition of claim 5, wherein the surfactant comprises a block copolymer of ethylene oxide and propylene oxide.
7. The composition of claim 1, wherein the lipid comprises a fatty acid glyceride ester.
8. The composition of claim 7, wherein the fatty acid glyceride ester comprises a monoglyceride or a triglyceride.
9. The composition of claim 8, wherein the fatty acid glyceride ester comprises a medium chain C<sub>6</sub>-C<sub>12</sub> fatty acid glyceride ester.

10. The composition of claim 9, wherein the medium chain C<sub>6</sub>-C<sub>12</sub> fatty acid glyceride ester is a triglyceride of caprylic/capric acid.

11. The composition of claim 1, wherein one or more of the humectants are selected from the group consisting of propylene glycol, 1,2-propanediol, and polyethylene glycol.

12. The composition of claim 11, wherein the polyethylene glycol has a molecular weight between 100 and 500 kDa.

13. The composition of claim 1, wherein one or more of the polymeric hydrogels are selected from the group consisting of natural gel-forming polymers or synthetic gel-forming polymers.

14. The composition of claim 13, wherein one or more of the natural gel-forming polymers are selected from the group consisting of carrageenan, xanthan gum, gum karaya, gum acaicia, locust bean gum, and guar gum.

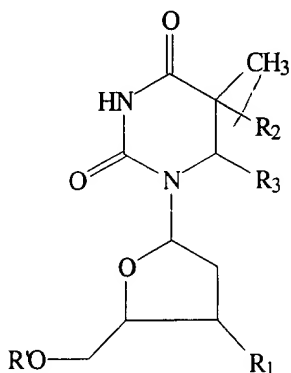
15. The composition of claim 14, wherein the natural gel-forming polymers are selected from the group consisting of carrageenan and xanthan gum.

16. The composition of claim 1, further comprising one or more preservatives.

17. The composition of claim 16, wherein one or more of the preservatives are selected from the group consisting of sodium benzoate, methyl parabens, propyl parabens, thimerisal, and sorbic acid.

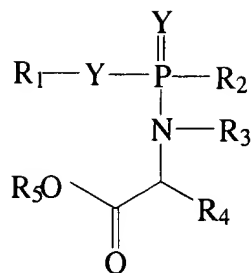
18. The composition of claim 19, wherein the preservative is sodium benzoate.

19. The composition of claim 1, in the form of a vaginal cream.
20. The composition of claim 1 further comprising one or more therapeutic agents.
21. The composition of claim 20, wherein one or more of the therapeutic agents are selected from the group consisting of antibacterial agents, antifungal agent, antiviral agents, and spermicidal agents.
22. The composition of claim 20, wherein the therapeutic agent is an AZT derivative.
23. The composition of claim 23, wherein the AZT derivative is a compound of formula:

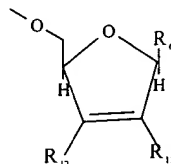
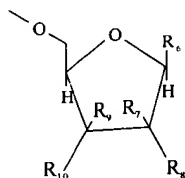


wherein  $R_1$  is H,  $N_3$ , halo, CN, COOH or  $NH_2$ ;  $R_2$  is halo;  $R_3$  is alkoxy; and  $R'$  is a group that facilitates the passage of the compound into a cell, or a pharmaceutically acceptable salt or ester thereof.

24. The composition of claim 23, wherein the AZT derivative is 5-bromo-6-methoxy-5,6-dihydro-3'-azidothymidine-5'-(p-bromophenyl)-methoxyalaninyl phosphate.
25. The composition of claim 20, wherein the therapeutic agent is a nucleoside derivative of the following formula:



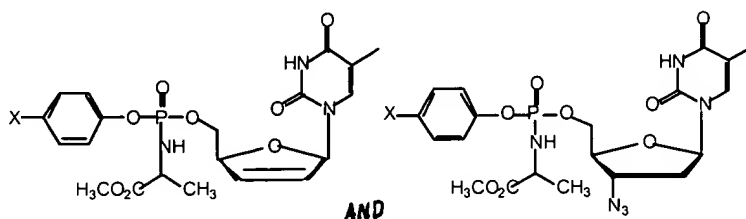
or a pharmaceutically acceptable salt thereof, in which Y is oxygen or sulfur; R<sub>1</sub> is unsubstituted aryl or aryl substituted with an electron-withdrawing group; R<sub>2</sub> is a nucleoside of one of the following formulae:



in which R<sub>6</sub> is purine or pyrimidine; and R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, R<sub>11</sub>, and R<sub>12</sub> are independently hydrogen, hydroxy, halo, azido, -NO<sub>2</sub>, -NR<sub>13</sub>R<sub>14</sub>, or -N(OR<sub>15</sub>)R<sub>16</sub>, in which R<sub>13</sub>, R<sub>14</sub>, R<sub>15</sub>, and R<sub>16</sub> are independently hydrogen, acyl, alkyl, or cycloalkyl;


R<sub>3</sub> is hydrogen, acyl, alkyl, or cycloalkyl; R<sub>4</sub> is a side chain of an amino acid; or R<sub>3</sub> and R<sub>4</sub> may be taken together to form the side chain of proline or hydroxyproline; and R<sub>5</sub> is hydrogen, alkyl, cycloalkyl, or aryl.

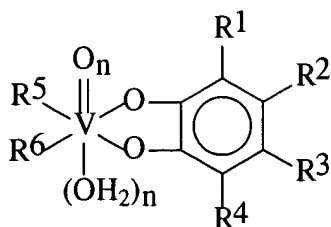
26. The composition of claim 25, wherein the nucleoside derivative is selected from those of the formula:




wherein X is an electron withdrawing group.

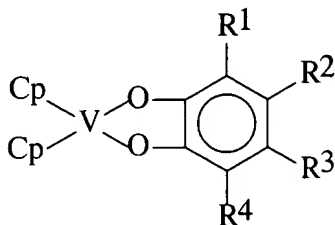
27. The composition of claim 26, wherein X is bromo or chloro.
28. The composition of claim 20, wherein the therapeutic agent comprises a vanadium (IV) complex, or a pharmaceutically acceptable salt thereof.
29. The composition of claim 28, wherein the vanadium (IV) complex comprises an organometallic cyclopentadienyl vanadium (IV) complex, or a pharmaceutically acceptable salt thereof.
30. The composition of claim 29, wherein the organometallic cyclopentadienyl vanadium IV complexes is selected from the following: vanadocene dichloride, bis (methylcyclopentadienyl) vanadium dichloride, vanadocene dibromide, vanadocene diiodide, vanadocene diazide, vanadocene dicyanide, vanadocene dioxycyanate, vanadocene dithiocyanate, vanadocene diselenocyanate, vanadocene ditriflate, vanadocene monochloro oxycyanate, vanadocene monochloroacetonitrilo tetrachloro ferrate, vanadocene acetylacetonato monotriflate, vanadocene bipyridino ditriflate, vanadocene hexafluoro acetylacetonato monotriflate, vanadocene acethydroxamato monotriflate, and vanadocene N-phenyl benzohydroxamato monotriflate.
31. The composition of claim 28, wherein the vanadium (IV) complex is an oxovanadium (IV) complex.
32. The composition of claim 31, wherein the oxovanadium (IV) complex includes at least one bidentate ligand selected from N,N'; N,O; and O,O' bidentate ligands.
33. The composition of claim 28, wherein the vanadium (IV) complex comprises a substituted or un-substituted catecholate ligand.

34. The composition of claim 33, wherein the vanadium (IV) complex is a complex having the structural formula: 



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are the same or different and are independently selected from H, halo, OH<sub>2</sub>, O<sub>3</sub>SCF<sub>3</sub>, N<sub>3</sub>, CN, OCN, SCN, SeCN, NO<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, and aryl; and n is 0 or 1; and R<sup>5</sup> and R<sup>6</sup> are the same or different and are either monodentate ligands or R<sup>5</sup> and R<sup>6</sup> together comprise a bidentate ligand.

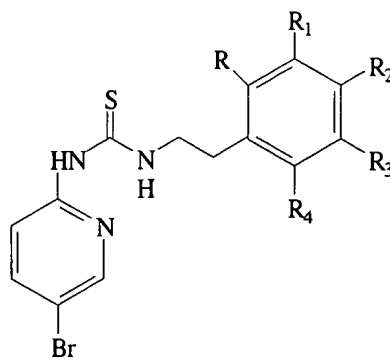
35. The composition of claim 34, wherein the vanadium (IV) complex is a complex having the structural formula: 



wherein Cp is unsubstituted cyclopentadienyl, or cyclopentadienyl substituted with one or more substituents selected from substituted or unsubstituted aryl, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halo, OH<sub>2</sub>, O<sub>3</sub>SCF<sub>3</sub>, N<sub>3</sub>, CN, OCN, SCN, SeCN, NO<sub>2</sub>;

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are the same or different and are independently selected from H, halo, OH<sub>2</sub>, O<sub>3</sub>SCF<sub>3</sub>, N<sub>3</sub>, CN, OCN, SCN, SeCN, NO<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>1</sub>-C<sub>4</sub> alkoxy.

36. A composition according to claim 20, wherein the therapeutic agent is a phenethyl-5-bromopyridylthiourea derivative of the following chemical formula, or a pharmaceutically acceptable salt thereof:

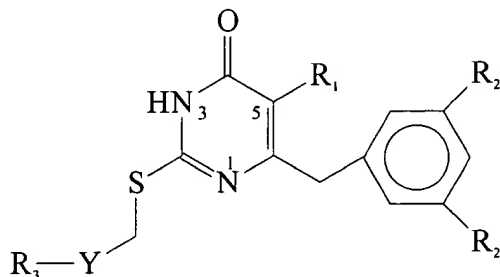


where R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> are independently hydrogen, F, Cl, Br, or I, and where at least one of R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> is F, Cl, Br, or I.

37. The composition of claim 36, wherein the phenethyl-5-bromopyridylthiourea derivative is selected from:

N-[2-(2-fluorophenethyl)]-N'-[2-(5-bromopyridyl)]-thiourea;  
 N-[2-(2-chlorophenethyl)]-N'-[2-(5-bromopyridyl)]-thiourea;  
 N-[2-(3-fluorophenethyl)]-N'-[2-(5-bromopyridyl)]-thiourea;  
 N-[2-(3-chlorophenethyl)]-N'-[2-(5-bromopyridyl)]-thiourea;  
 N-[2-(4-fluorophenethyl)]-N'-[2-(5-bromopyridyl)]-thiourea;  
 N-[2-(4-chlorophenethyl)]-N'-[2-(5-bromopyridyl)]-thiourea; and  
 mixtures thereof.

38. A composition according to claim 20, wherein the therapeutic agent is a dihydroxalkoxybenzylpyrimidine derivative of the following chemical formula, or a pharmaceutically acceptable salt thereof:



where  $R_1$  and  $R_2$  are alike or different, and are hydrogen, halo, alkyl, alkenyl, hydroxy, alkoxy, thioalkyl, thiol, phosphino, ROH, or RNH group, where R is alkyl; Y is S or O; and  $R_3$  is alkyl, alkenyl, aryl, aralkyl, ROH, or RNH group, where R is alkyl.

39. The composition of claim 38, wherein the dihydroxalkoxybenzylpyrimidine derivative is selected from:

5-methyl-2-[(methylthiomethyl)thio]-6-benzyl-pyrimidin-4-1H-one,

5-ethyl-2-[(methylthiomethyl)thio]-6-benzyl-pyrimidin-4-1H-one,

5-isopropyl-2-[(methylthiomethyl)thio]-6-benzyl-pyrimidin-4-1H-one,

5-isopropyl-2-[(methylthiomethyl)thio]-6-(3,5-dimethylbenzyl)-pyrimidin-4-1H-one;

and

mixtures thereof.

40. The composition of claim 1, wherein the composition has a viscosity in the range of about 200 to about 1000 centipoise.



41. The composition of claim 1, wherein the composition has a submicron partical size in the range of about 30 to about 80 nm.

42. The composition of claim 1, wherein the composition comprises:  
in the range of about 2% ~~to~~ about 25% by weight lipid;  
in the range of about 3% to about 30% by weight surfactant;  
in the range of about 2% to about 24% humectant;  
in the range of about 0.5% to about 4% polymer gel; and  
in the range of about 0% to about 0.5% preservative.

43. The composition of claim 1, wherein the composition comprises:  
in the range of about 6% ~~to~~ about 23% by weight lipid;  
in the range of about 4% to about 17% by weight surfactant;  
in the range of about 3% to about 12% humectant;  
in the range of about 1% to about 2% polymer gel; and  
in the range of about 0% to about 0.3% preservative.

44. The composition of claim 1, wherein the composition comprises:  
in the range of about 8% ~~to~~ about 15% by weight lipid;  
in the range of about 8% to about 15% by weight surfactant;  
in the range of about 5% to about 10% humectant;  
in the range of about 1.2% to about 1.8% polymer gel; and  
in the range of about 0% to about 0.2% preservative.

45. The composition of claim 1, wherein the composition comprises:  
in the range of about 2% to about 20% by weight lipid;  
in the range of about 4% to about 17% by weight surfactant;  
in the range of about 5% to about 22% humectant;  
in the range of about 0.5% to about 2% polymer gel; and

in the range of about 0.1% to about 0.3% preservative.

46. The composition of claim 1, wherein the composition comprises:  
in the range of about 3% to about 10% by weight lipid;  
in the range of about 4% to about 10% by weight surfactant;  
in the range of about 12% to about 19% humectant;  
in the range of about 0.8% to about 1.2% polymer gel; and  
in the range of about 0.15% to about 0.2% preservative.
47. The composition of claim 1, wherein the composition comprises:  
in the range of about 6% to about 23% medium chain C<sub>6</sub>-C<sub>12</sub> triglyceride;  
in the range of about 3% to about 10% ethoxylated castor oil;  
in the range of about 1.5 % to about 6% phospholipid;  
in the range of about 1.5% to about 6% propylene glycol;  
in the range of about 1.5% to about 6% polyethylene glycol;  
in the range of about 1% to about 2% natural polymer gel; and  
in the range of about 0% to about 0.2% preservative.
48. The composition of claim 1, wherein the composition comprises:  
in the range of about 8% to about 15% medium chain C<sub>6</sub>-C<sub>12</sub> triglyceride;  
in the range of about 5% to about 9% ethoxylated castor oil;  
in the range of about 3 % to about 6% phospholipid;  
in the range of about 3% to about 6% propylene glycol;  
in the range of about 3% to about 6% polyethylene glycol;  
in the range of about 1.2% to about 1.8% natural polymer gel; and  
in the range of about 0.1% to about 0.2% preservative.
49. The composition of claim 1, wherein the composition comprises:  
in the range of about 2% to about 20% medium chain C<sub>6</sub>-C<sub>12</sub> triglyceride;

in the range of about 1% to about 10% ethoxylated castor oil;  
in the range of about 0.2% to about 1% block copolymer of ethylene oxide and propylene oxide;  
in the range of about 1 % to about 10% phospholipid;  
in the range of about 2% to about 22% propylene glycol;  
in the range of about 0.6% to about 2% natural polymer gel; and  
in the range of about 0% to about 0.3% preservative.

50. The composition of claim 1, wherein the composition comprises:  
in the range of about 3% to about 10% medium chain C<sub>6</sub>-C<sub>12</sub> triglyceride;  
in the range of about 2% to about 5% ethoxylated castor oil;  
in the range of about 0.2% to about 0.8% block copolymer of ethylene oxide and propylene oxide;  
in the range of about 1 % to about 5% phospholipid;  
in the range of about 12% to about 19% propylene glycol;  
in the range of about 0.8% to about 1.2% natural polymer gel; and  
in the range of about 0% to about 0.2% preservative.

51. The composition of claim 47 further comprising one or more therapeutic agents.

52. The composition of claim 51 wherein the therapeutic agent comprises up to 10% by weight of the composition.

53. A process for preparing a pharmaceutical composition according to claim 1, the process comprising:

- (a) combining surfactants, hydrophilic components, and lipids in a container;
- (b) mildly heating and mixing the combined the components until a clear and homogeneous micoremulSION is formed;

- (c) removing the microemulsion from heat and allowing to cool to about room temperature;
- (d) adding two parts of a pre-prepared polymer dispersion to each part of microemulsion; and
- (e) mixing the polymer dispersion and microemulsion to form the composition of claim 1.

54. The process of claim 53, wherein the composition has a viscosity in the range of about 200 centipoise to about 1000 centipoise.

55. The process of claim 53, wherein the composition has a submicron particle size in the range of about 30 nm to about 80 nm.

56. A process for making the composition of claim 20, the process comprising:

- (a) combining surfactants, hydrophilic components, and lipids in a container;
- (b) mildly heating and mixing the combined components until a clear and homogeneous microemulsion is formed;
- (c) adding one or more therapeutic agents to the microemulsion and mixing until the drug is solubilized in the microemulsion;
- (c) removing the microemulsion with solubilized therapeutic agent(s) from heat and allowing to cool to about room temperature;
- (d) adding two parts of a pre-prepared polymer dispersion to each part of microemulsion; and
- (e) mixing the polymer dispersion and microemulsion to form the composition of claim 20.

57. The process of claim 56, wherein the resulting composition has a viscosity in the range of about 200 centipoise to about 1000 centipoise.

58. The process of claim 56, wherein the resulting composition has a submicron particle size in the range of about 30 ~~nm~~ to about 80 nm.

59. A method for inhibiting the motility of sperm, the method comprising:

a) providing a pharmaceutical composition comprising a gel-microemulsion comprising an oil-in-water microemulsion and a polymeric hydrogel, wherein the oil-in-water microemulsion comprises a medium chain C<sub>6</sub>-C<sub>12</sub> fatty acid glyceride ester, one or more pharmaceutically acceptable surfactants, one or more pharmaceutically acceptable humectants, and water as a diluent; and

b) contacting the sperm with the pharmaceutical composition.

60. The method of claim 59, wherein the pharmaceutical composition further comprises a spermicidal agent.

61. The method of claim 59, wherein the sperm is contacted with the pharmaceutical composition intravaginally.

62. ✓ A pharmaceutical composition adapted for the topical delivery of a therapeutic agent, the composition comprising a gel-microemulsion comprising an oil-in-water microemulsion and a polymeric hydrogel; and

an effective amount of a therapeutic agent, wherein the gel-microemulsion acts as a formulation base for delivery of the therapeutic agent, wherein

the oil-in-water microemulsion comprises a medium chain C<sub>6</sub>-C<sub>12</sub> fatty acid glyceride ester, one or more pharmaceutically acceptable surfactants, one or more pharmaceutically acceptable humectants, and water as a diluent.

63. The composition of claim 62, wherein;

the medium chain C<sub>6</sub>-C<sub>12</sub> fatty acid glyceride ester comprises a medium chain tryglyceride;

the surfactant comprises phospholipid and a nonionic surfactant;  
the humectant comprises propylene glycol; and  
the polymer gel comprises a natural polymer gel.

64. The composition of claim 63, wherein the nonionic surfactant is selected from the group consisting of ethoxylated castor oil and block copolymer of ethylene oxide and propylene oxide.
65. The composition of claim 63, wherein the humectant further comprises polyethylene glycol.
66. The composition of claim 63, further comprising a preservative.
67. The composition of claim 62, wherein the pharmaceutical composition comprises:  
up to about 10% by weight of therapeutic agent;  
in the range of about 2% to about 25 % by weight lipid;  
in the range of about 3% to about 30 % by weight surfactant;  
in the range of about 2% to about 24 % by weight humectant;  
in the range of about 0.5% to about 4 % by weight polymer gel;  
in the range of about 0% to about 0.5% preservative.
68. The composition of claim 62, wherein the pharmaceutical composition comprises:  
up to about 5% by weight of therapeutic agent;  
in the range of about 6% to about 23 % by weight lipid;  
in the range of about 4% to about 17 % by weight surfactant;  
in the range of about 3% to about 12 % by weight humectant;  
in the range of about 1% to about 2 % by weight polymer gel;  
in the range of about 0.1% to about 0.3% preservative.

69. The composition of claim 62, wherein the pharmaceutical composition comprises:  
up to 2% by weight of therapeutic agent;  
in the range of about 8% to about 15 % by weight lipid;  
in the range of about 8% to about 15 % by weight surfactant;  
in the range of about 5% to about 10 % by weight humectant;  
in the range of about 1.2% to about 1.8 % by weight polymer gel;  
in the range of about 0.15% to about 0.2% preservative.
70. The composition of claim 62, wherein the pharmaceutical composition comprises:  
up to about 5% by weight of therapeutic agent;  
in the range of about 2% to about 20 % by weight lipid;  
in the range of about 4% to about 17 % by weight surfactant;  
in the range of about 5% to about 22 % by weight humectant;  
in the range of about 0.6% to about 2 % by weight polymer gel;  
in the range of about 0% to about 0.3% preservative.
71. The composition of claim 62, wherein the pharmaceutical composition comprises:  
up to about 2% by weight of therapeutic agent;  
in the range of about 3% to about 10 % by weight lipid;  
in the range of about 4% to about 10 % by weight surfactant;  
in the range of about 12% to about 19 % by weight humectant;  
in the range of about 0.8% to about 1.2 % by weight polymer gel;  
in the range of about 0% to about 0.2% by weight preservative.
72. The composition of claim 62, wherein one or more the therapeutic agents are selected from the group consisting of an anti-microbial agent and a spermicidal agent.
73. The composition of claim 72, wherein the composition comprises  
up to about 2% anti-microbial agent, spermicidal agent, or combinations thereof;

in the range of about 2% to about 20% by weight medium chain C<sub>6</sub>-C<sub>12</sub> triglyceride;  
in the range of about 1% to about 10% by weight ethoxylated castor oil;  
in the range of about 0.2% to about 1% by weight block copolymer of ethylene oxide  
and propylene oxide;  
in the range of about 1% to about 10% by weight phospholipid;  
in the range of about 5% to about 22% by weight propylene glycol;  
in the range of about 0.6% to about 2% by weight natural hydrogel; and  
in the range of 0% to about 0.3% preservative.